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HDL and LDL cholesterol, but the atherosclerotic lesion size in the aortic root remained unchanged. Surprisingly, the highly oxidized diet was not associated with an increase in biomarkers of lipid peroxidation, including F₂-isoprostanes and malondialdehyde, despite the higher consumption of acrolein, hexanal, trans-2-octenal, trans-2-nonenal, 2,4-decadienal. Furthermore, levels of the inflammatory cytokines IL-6, TNF-alpha and MCP-1 were lowest in the high oxidation group. In conclusion, chronic intake of PUFA oxidation products did not promote changes in oxidative stress biomarkers or atherosclerosis in LDLr^(-/-) mice.

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Protein Disulfide Isomerase-A1 Overexpression Attenuates Vascular Calcification in Vivo

Luciana Pescatore¹, Patricia Nolasco¹, Melissa Fessel², Youri Almeida², João Wosniak Jr¹, Victor Debbas¹, Lionel Gamarra², Marcel Liberman², Francisco R Laurindo³

¹Heart Institute/ FMUSP, Brazil, ²Hospital Israelita Albert Einstein, Brazil, ³University of São Paulo, Brazil

Vascular calcification (VC) is an active pathophysiological process without effective therapy. Endoplasmic reticulum (ER) stress and oxidative stress support VC progression. Oxidant levels, expression of Nox subunits and ER redox chaperone protein disulfide isomerase-A1 (PDI) are upregulated in calcifying rabbit valves. We hypothesized that PDI protects against VC. Our group developed a new PDI overexpression mouse model (TgPDI) in FVB background (WT). To investigate whether TgPDI mice protect against VC, we challenged 20-week-old TgPDI (n=7) or WT (n=6) mice with Vitamin-D3 (VitD, 9x10⁴ IU/day) for 14 days and compared to paired untreated mice (n=8). Cross-sectional aortae, stained with Alizarin Red S, showed increased calcium deposition in WT/VitD (53% fractional area) vs. WT mice, which was not present in TgPDI and in TgPDI/VitD mice (<5% fractional area). *In vivo* Bone Tag[®] injection confirmed increased VC in WT/VitD mice compared to WT mice, which was abrogated in TgPDI/VitD. Positive correlation between vascular calcification and remodeling (total vascular area) was confirmed by correlation analysis (r²=0.92, p<0.001). Osteogenic markers like Osterix, MSX2 and BMP2 were augmented in WT/VitD vs. WT, but not in TgPDI/VitD. Furthermore, decreased SM22 expression in both WT/VitD or TgPDI/VitD vs. paired untreated mice, depicts loss of vascular smooth muscle cell (VSMC) contractile phenotype. However, Calponin expression was decreased only in WT/VitD vs. untreated WT mice. ER stress assessment demonstrated increased GRP78 expression only in WT/VitD. Cell death (Tunel) was evident only in aortae from WT/VitD mice. MGP, a VC-inhibiting protein, and total γ-Carboxyglutamyl were increased in WT/VitD but not in TgPDI/VitD mice, probably by a protective mechanism. Moreover, elastic fiber rupture and collagen deposition increased only in WT/VitD mice. In conclusion, PDI overexpression *in vivo* protected against VC and expansive vascular remodeling progression in our model.

PDI and respective molecular signaling deserve further study as potential therapeutic target in VC progression.

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Tempol Treatment of Covid-19

Peter Proctor

Drugscom, Houston, TX, USA

Presentation: A septuagenarian male experienced sudden frightening onset of severe headache, marked nausea and vomiting, pharyngitis, severe upper respiratory congestion, fever, chills, weakness, malaise, and mild pulmonary congestion. O₂ saturation=96%. Presumptive-diagnosis: "Covid-19". Treatment: Nausea and vomiting continued without respite for several hours. Anti-nausea tablets were twice regurgitated intact. Accordingly, treatment was initiated with 30 mg of the SOD-mimetic antioxidant drug [Tempol](#) PO as the hydroxylamine in a 6% water solution containing 90 mg vitamin-C. Patient kept this down. Along with Tempol-zinc gargles for pharyngitis, intranasal treatment was then initiated with a medication-soaked cotton swab and insufflation, repeated q 6h as symptoms returned. This was followed by similar doses of Tempol-H three and six hours later, repeated BID PO for the next ten days. On days 2-3, treatment was briefly initiated with hydroxychloroquine, zinc, doxycycline, ivermectin, and famotidine, then withdrawn. Results: Within one-hour post-Tempol-H, vomiting ceased, headache eased significantly, and the patient felt objectively better. Nasal congestion also reversibly eased upon intranasal treatment. By days 5-7 remaining symptoms were mild reversible-on-treatment nasal congestion, pharyngitis, and malaise. Excepting slight malaise, patient was essentially asymptomatic by days 8-9. As expected, PCR was negative day 10. Although the diagnosis is reasonably sure, IgG was negative at days 11 and 58. Conclusions: The usual objections to N=1 case-reports apply. However, the almost immediate relief of gastrointestinal symptomatology was striking and arguably reflects some direct action of Tempol-H on coronavirus-infected gastric mucosa, as does the effect on nasal mucosa. Minimally, Tempol/Tempol-H may be used with relative safety and arguable effectiveness in presumptive early Covid-19. Similarly, we have used Tempol without incident for decades, e.g., for treatment of fibrocystic disease, breast cancer prophylaxis, respiratory infections, and for alopecia, a classic redox-signaling-mediated process. Significantly, both pattern balding and stress-induced hair-loss are strongly-associated with Covid-19, perhaps reflecting pre-existing or Covid-19-induced oxidative stress.

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